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The Impact of Renin-Angiotensin-Aldosterone System Blockade on Heart Failure Outcomes and Mortality in Patients Identified to Have Aortic Regurgitation

A Large Population Cohort Study

Douglas H. J. Elder,* Li Wei, PhD, MPH,† Benjamin R. Szwejkowski,* Renata Libianto, MBBS,‡ Adnan Nadir,* Maheshwar Pauriah,* Sushma Rekhraj,* Tiong K. Lim, MD,* Jacob George, MD,* Alex Doney, PhD,* Stuart D. Pringle, MD,* Anna-Maria Choy, MD,* Allan D. Struthers, MD,* Chim C. Lang, MD*

Dundee, United Kingdom; and Melbourne, Australia

Objectives The aim of this study was to investigate the effect of renin-angiotensin system blockade on outcomes in patients with aortic regurgitation (AR).

Background Angiotensin-converting enzyme (ACE) inhibitors have the potential to reduce afterload, blunt left ventricular wall stress, and limit left ventricular dilation and hypertrophy. However, long-term studies have yielded inconsistent results, and very few have assessed clinical outcomes.

Methods The Health Informatics Centre dispensed prescription and morbidity and mortality database for the population of Tayside, Scotland, was linked through a unique patient identifier to the Tayside echocardiography database. Patients diagnosed with at least moderate AR from 1993 to 2008 were identified. Cox regression analysis was used to assess differences in all-cause mortality and cardiovascular (CV) and AR events (heart failure hospitalizations, heart failure deaths, or aortic valve replacement) between those treated with and without ACE inhibitors or angiotensin receptor blockers (ARBs).

Results A total of 2,266 subjects with AR (median age 74 years; interquartile range: 64 to 81 years) were studied, with a mean follow-up period of 4.4 ± 3.7 years. Seven hundred and five patients (31%) received ACE inhibitor or ARB therapy. There were 582 all-cause deaths (25.7%). Patients treated with ACE inhibitors or ARBs had significantly lower all-cause mortality and fewer CV and AR events, with adjusted hazard ratios of 0.56 (95% confidence interval [CI]: 0.64 to 0.89; $p < 0.01$) for all-cause mortality, 0.77 (95% CI: 0.67 to 0.89; $p < 0.01$) for CV events, and 0.68 (95% CI: 0.54 to 0.87; $p < 0.01$) for AR events.

Conclusions This large retrospective study shows that the prescription of ACE inhibitors or ARBs in patients with moderate to severe AR was associated with significantly reduced all-cause mortality and CV and AR events. These data need to be confirmed by a prospective randomized controlled outcome trial. (J Am Coll Cardiol 2011;58:2084–91)

Chronic aortic regurgitation (AR) is a common valvular heart disease and has been reported to occur in up to 10% of the middle-aged to older population who undergo echocardiography (1). The most common etiologies include aortic dilation, congenital bicuspid valves, and hypertension. AR results in slow and insidious left ventricular (LV) dilation, with a long asymptomatic phase (2–4). AR is important because approximately 6% of patients with AR progress to symptoms of LV systolic dysfunction (LVSD) or LV dilation each year, and the mortality rate is approximately 10% per year in the presence of LVSD (5).

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From the *Centre for Cardiovascular and Lung Biology, Ninewells Hospital and Medical School, Dundee, United Kingdom; †Medicines Monitoring Unit, University of Dundee, Dundee, United Kingdom; and the ‡University of Melbourne, Melbourne, Australia. This study was supported by Tenovus Scotland (Glasgow, United Kingdom). Dr. Choy has received modest research funding from St. Jude Medical and has served as a consultant for Sanofi-Aventis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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In the early stages of AR, normal stroke volume is usually maintained, because the left ventricle can respond well to the increasing pressure and volume load created by the incompetent valve (6). Increases in end-diastolic volume, wall compliance, and LV hypertrophy occurring without increases in filling pressures allow the left ventricle to continue to maintain normal stroke volume (7). Progression of AR results in increases in systolic wall stress, a combination of volume and pressure overload ensue, and this increased LV afterload leads to further LV hypertrophy, while still maintaining a normal stroke volume (8). It is in this plateau phase, when the left ventricle is able to maintain normal cardiac output because of enhanced LVH despite increased afterload, that vasodilators are thought to have a role (9,10). In short-term studies examining their effects, vasodilators had been previously shown to reduce AR volume (9,11) and improve LV hemodynamic parameters (10–16). However, longer term studies have yielded conflicting results, and very few have assessed clinical outcomes (15,17–19). The current American College of Cardiology and American Heart Association 2006 guidelines recommend the use of vasodilators only in patients with hypertension with chronic, severe AR, with the goal of reducing systolic blood pressure (20). Importantly the guidelines do not recommend vasodilators as routine therapy in the absence of systolic hypertension or in asymptomatic patients with normal LV function. This reflects the paucity of clinical data and the heterogeneity of the findings of contemporary data. Importantly, there has been no study of the impact of vasodilators on survival.

In an animal model of chronic AR, Plante et al. (21) demonstrated abnormal activation of the renin-angiotensin system (RAS), which might suggest that blocking this system could play an important role in preventing LV dilation, hypertrophy, and loss of systolic function (21). Recently, again using a rat model, the same investigators showed that vasodilators targeting the RAS (captopril and losartan) were more effective than nifedipine in slowing the development of LV remodeling and preserving LV function (22). Because of the lack of evidence on whether angiotensin-converting enzyme (ACE) inhibitors improve survival in AR, we sought to investigate the potential survival benefits of ACE inhibitors or angiotensin receptor blockers (ARBs) in a large retrospective observational cohort of patients identified to have moderate to severe AR by echocardiography.

Methods

Study design. This was a retrospective, population-based, longitudinal cohort study. Data on all patients with new diagnoses of AR were ascertained from a clinical echocardiographic database (>110,000 scans) maintained by the cardiology department at Ninewells Hospital (Tayside, Scotland). These echocardiographic data were then linked anonymously using a unique patient-specific identifier, the Community Health Index Number, to the Medicines Monitoring Unit database of community-dispensed prescriptions maintained by the Health Informatics Centre at the University of Dundee, which contains detailed prescribing information on all residents of Tayside (population >400,000) since 1993, as previously described (23). Other clinical datasets included laboratory test results, hospital admissions (Scottish Morbidity Record), and mortality data (General Registry Office). Access to the anonymized and validated clinical datasets was administered by the Health Informatics Centre at the University of Dundee using established protocols approved by the Research Ethics Committee in Tayside.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AR = aortic regurgitation
ARB = angiotensin receptor blocker
AVR = aortic valve replacement
CI = confidence interval
CV = cardiovascular
HR = hazard ratio
ICD-9 = International Classification of Diseases-Ninth Revision
ICD-10 = International Classification of Diseases-Tenth Revision
LV = left ventricular
LVSD = left ventricular systolic dysfunction
RAS = renin-angiotensin system

Study patients. All patients diagnosed with at least moderate AR were identified from the echocardiographic database from September 1993 to July 2008. The diagnosis and severity of AR were ascertained by British Society of Echocardiography–accredited sonographers at the time of the scan using approved techniques, including jet dimensions within the LV outflow tract, the direction of flow within the descending aorta, and pressure half-time. Patients were entered into the study from the date of the first echocardiographic study with a diagnosis of AR and were censored when they underwent aortic valve replacement (AVR), had a cardiovascular (CV) cause of admission to the hospital, died, or left the region, as appropriate. Patients with histories of malignancy were excluded from the study. Patients in the ACE inhibitor or ARB cohort (cases) were those who had 2 or more dispensed prescriptions for ACE inhibitors or ARBs during the follow-up period. All other patients who were never prescribed ACE inhibitors or ARBs were analyzed as the control cohort.

Outcomes. The primary outcome was defined as all-cause mortality, with secondary outcomes of CV events (CV death or hospitalization) and AR events (heart failure hospitalization, heart failure death, or AVR). Hospitalizations were ascertained from the Scottish Morbidity Record database; CV hospitalization was defined by primary International Classification of Diseases-Ninth Revision (ICD-9) codes (410, 411, 413, 428, and 430 to 438) and International Classification of Diseases-Tenth Revision (ICD-10) codes (I20 to I22, I50, and I60 to I64) for myocardial infarction, angina, heart failure, cerebrovascular accident, atherosclerosis, and aortic aneurysm, and heart failure hos-

Table 1 Baseline Characteristics

Variable	All	No ACE Inhibitors	ACE Inhibitors	p Value (ACE Inhibitors vs. No ACE Inhibitors)
n	2,266	1,390 (61.34%)	876 (38.66%)	
Age (yrs)	74 (64–81)	75 (66–82)	72 (63–79)	<0.001
Men	902 (40%)	526 (37.84%)	376 (42.9%)	0.02
BMI (kg/m^2)	25 (23–29)	25.4 (23–29)	26 (23–29)	0.87
SBP (mm Hg)	142 (130–160)	140 (130–157)	140 (130–160)	0.68
DBP (mm Hg)	73 (65–82)	75 (64–81)	75 (65–82)	0.71
Hemoglobin (mg/dl)	12.7 (11.6–14)	12.8 (11.4–13.9)	13 (11.8–13.9)	<0.001
Cholesterol (mmol/l)	4.90 (4.13–5.74)	4.88 (4.17–5.74)	4.9 (4.1–5.75)	0.73
Creatinine (mmol/l)	98 (84–120)	97 (83–121)	99 (85–117)	0.98
LVISD (cm)	3.03 ± 2.58	2.88 ± 2.54	3.28 ± 2.62	<0.001
Diabetes	298 (13%)	154 (11.07%)	144 (16.44%)	<0.001
Renal admission	60 (3%)	35 (2.52%)	25 (2.85%)	0.63
COPD	79 (3%)	50 (3.6%)	29 (3.31%)	0.72
Previous event	625 (28%)	313 (22.52%)	312 (35.62%)	<0.001
Aspirin	1,154 (51%)	594 (51.47%)	560 (63.93%)	<0.001
Diuretic agents	545 (24%)	301 (21.6%)	244 (27.90%)	<0.001
Beta-blockers	789 (35%)	389 (27.98%)	400 (45.66%)	<0.001
Calcium antagonists	774 (34%)	407 (29.28%)	367 (40.96%)	<0.001
Digoxin	528 (23%)	283 (20.40%)	245 (27.97%)	<0.001
Nitrates	705 (31%)	331 (23.81%)	374 (42.69%)	<0.001
Statins	870 (38%)	369 (26.55%)	501 (57.19%)	<0.001
LV impairment	1,030 (45%)	642 (46.18%)	388 (44.29%)	0.38

Values are n (%), median (interquartile range), or mean ± SD.

ACE = angiotensin-converting enzyme; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; LV = left ventricular; LVISD = left ventricular internal systolic diameter; SBP = systolic blood pressure.

pitalization was defined by ICD-9 code 428 and ICD-10 code I50. The main cause of death was ascertained from the General Registry Office database, with CV death defined as diseases of the circulatory system (ICD-9 codes 390 to 459 and ICD-10 codes I00 to I99) and heart failure death defined as ICD-9 code 428 and ICD-10 code I50.

Statistical analyses. For comparison of baseline variables, categorical data were analyzed using chi-square tests and continuous variables using nonparametric Mann-Whitney *U* tests. For the longitudinal outcome analysis, Kaplan-Meier survival curves were generated, and the differences between survival distributions were assessed using log-rank tests. The effects of known prognostic clinical and echocardiographic variables were examined using Cox proportional hazards regression analysis including age, sex, social deprivation category, LV function, LV dimension, diabetes, renal function, CV history, and concurrent use of CV drugs as covariates. We performed several sensitivity analyses. First, to minimize confounding influences, we determined a propensity score (a conditional probability of exposure to a treatment given observed covariates) using a logistic regression model. We subsequently used the score to perform a subgroup analysis in which cohorts of subjects exposed or not exposed to ACE inhibitors or ARBs were matched for propensity, with a tolerance of 0.05. Second, the association between ACE inhibitor or ARB use and CV events was assessed using a Cox regression model with a time-dependent variable for ACE inhibitor or ARB use. Third, given the likely bias caused by the prescription of ACE inhibitors to those with LVSD, we performed subgroup analyses comparing patients with normal LV function and those with LVSD and similarly in those with and without dilated left ventricles on the basis of diastolic LV dimensions. Additionally, we also performed subgroup analysis by severity of AR in the subgroup of patients in whom blood pressure data were available. All statistical analyses were performed by skilled statisticians using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina), and 2-sided p values <0.05 were considered significant.

Results

Patient characteristics. A total of 2,266 patients with moderate to severe AR were included in the study, with a median age of 74 years (interquartile range: 64 to 81 years); 40% were men. Eight hundred seventy-six (39%) were treated with ACE inhibitors. The baseline characteristics of the population are shown in Table 1. Continuous variables are presented as mean ± SD or as medians (interquartile ranges), while categorical variables are shown as percents. Those treated with ACE inhibitors or ARBs were younger (70 years vs. 72 years, $p = 0.01$) and more likely to be male. They were also more likely to have LVSD, diabetes, or previous CV events, and to be prescribed other CV medications. There was no significant difference in blood pressure between the 2 groups at baseline.

Table 2 Study Outcomes With Adjusted HRs

Outcome Event	All Patients	ACE Inhibitors or ARBs	No ACE Inhibitors or ARBs	HR (95% CI)
All-cause mortality	582 (26%)	127 (15%)	455 (33%)	0.56 (0.46–0.68)
CV events (CV death or hospitalization)	1,069 (47%)	344 (39%)	725 (52%)	0.77 (0.67–0.89)
AR events (HF hospitalization, HF death, or AVR)	354 (17%)	155 (18%)	199 (14%)	0.74 (0.56–0.96)

Values are n (%) unless otherwise indicated.

ACE = angiotensin-converting enzyme; AR = aortic regurgitation; ARB = angiotensin receptor blocker; AVR = aortic valve replacement; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.

Outcomes. During a mean follow-up period of 4.4 ± 3.7 years, there were 582 deaths (26%), 1,069 CV events (47%; CV death or hospitalization), and 354 AR events (16%). Sixty-five patients (2.7%) underwent AVR during follow-up. Of the 876 patients (39%) who were treated with ACE inhibitors or ARBs, 344 (39%) had CV events, 155 (18%) had AR events, and all-cause mortality occurred in 127 (15%). Among patients not treated with ACE inhibitors or ARBs, 725 (53%) had CV events, 199 (14%) had AR events, and there were 455 deaths (33%). In the Cox regression analysis, the adjusted hazard ratio (HR) associated with the use of ACE inhibitors or ARBs for CV events was 0.77 (95% confidence interval [CI]: 0.67 to 0.89; $p < 0.01$). The adjusted HR associated with the use of ACE inhibitors or ARBs for all-cause mortality was 0.56 (95% CI: 0.46 to 0.68; $p < 0.001$) (Table 2). The time-dependent analysis showed similar findings, with adjusted HRs for CV events and mortality of 0.45 (95% CI: 0.21 to 0.99) and 0.18 (95% CI: 0.06 to 0.54), respectively. Considering AR events, the HR for those treated with ACE inhibitors or ARBs was 0.68 (95% CI: 0.54 to 0.87; $p < 0.01$) compared with those not treated. The Kaplan-Meier curves for all-cause mortality, CV events, and AR events in patients with compared with those without ACE inhibitor or ARB therapy are shown in Figure 1.

In the subgroup analysis based on LV dimensions, patients with LV diastolic dimensions >6 cm had the largest benefit with ACE inhibitor therapy: for LV diastolic dimension <6 cm, the HR was 0.77 (95% CI: 0.67 to 0.90; $p < 0.01$), and for LV diastolic dimension >6 cm, the HR was 0.52 (95% CI: 0.32 to 0.86; $p < 0.001$) for all-cause mortality. In patients with LVSD, the HRs for all-cause mortality in those treated with ACE inhibitors or ARBs compared with those not treated were 0.56 (95% CI: 0.43 to 0.74; $p < 0.001$) for normal LV function, 0.28 (95% CI: 0.17 to 0.47; $p = 0.01$) for moderate LVSD, and 0.52 (95% CI: 0.27 to 1.0; $p = 0.04$) for severe LVSD.

Degree of regurgitation. We stratified outcome data on the basis of the echocardiographers' assessments of AR severity. The beneficial effects on all-cause mortality of ACE inhibitor therapy were seen in patients with both moderate and severe regurgitation, but the survival benefit was most marked in the severe group (HR: 0.4; 95% CI: 0.24 to 0.66; $p < 0.01$), as shown in Table 3.

Propensity score–matched cohort analysis. To minimize the potential bias inherent in post-discharge prescriptions of ACE inhibitors, and to address the effects of imbalanced covariants at baseline, we used a propensity score–matched cohort analysis (24,25). The C statistic for the separation of the groups in the regression model was 0.62. The cohort consisted of 1,702 patients, with 851 patients in each group (Table 4). The HRs in this analysis were 0.57 (95% CI: 0.41 to 0.79) for CV events, 0.73 (95% CI: 0.57 to 0.95; $p < 0.01$) for AR events, and 0.39 (95% CI: 0.22 to 0.67; $p < 0.01$) for all-cause mortality (Table 5).

Discussion

The medical management of patients with severe AR remains controversial. Clinical trials focusing on AR are rare, with 2 studies that have examined the impact of vasodilators on clinical outcome in patients with chronic AR. Scognamiglio et al. (26) randomized 143 asymptomatic patients with chronic, severe AR to either nifedipine or digoxin. At the end of 6 years, patients treated with nifedipine had a significantly lower rate of progression to AVR than those treated with digoxin. Post-operative LV ejection fractions after AVR were reported to be significantly higher in patients treated with nifedipine than with digoxin. These findings contrast with those from a study by Evangelista et al. (19) that investigated the effect of enalapril (20 mg/day), nifedipine (20 mg), or no treatment in an open-label study involving 95 patients with asymptomatic severe AR. After a mean follow-up period of 7 years, there was no difference in any of the groups during follow-up in the time to AVR, AR volume, or LV function on echocardiography. Considering these conflicting data and the paucity of clinical data (a total of 238 patients enrolled), the American Heart Association and American College of Cardiology valvular heart disease treatment guidelines no longer recommend any vasodilator for the medical management of chronic AR in patients with normal ventricular function. Importantly, there has been no outcome study investigating the impact of ACE inhibitors or vasodilators on survival. In this study, we used a well-tested bioinformatics platform with record linkage of an echocardiographic database to prescribing and outcomes data (23) to identify a total of 2,266 subjects with moderate to severe AR and examined the impact of vasodilator therapy on outcome. The mean follow-up period was 4.5 years. We have shown that in patients with AR, the prescription of ACE inhibitors or ARBs significantly reduced all-cause mortality, CV

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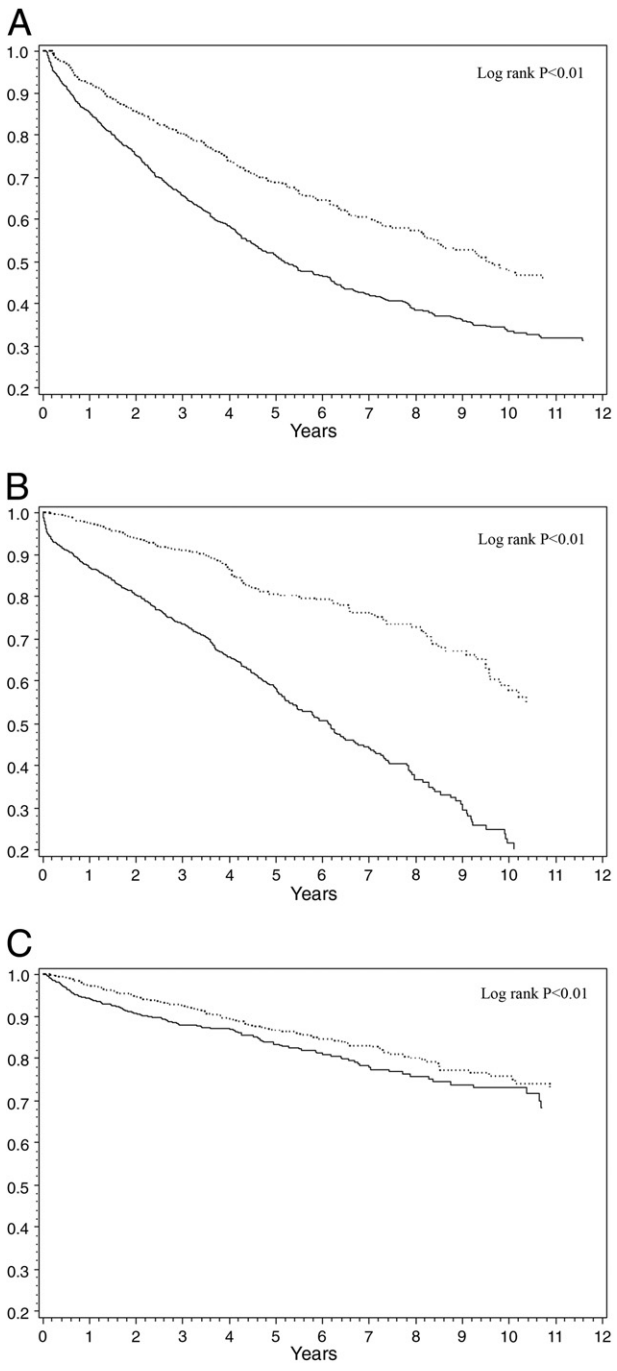

Figure 1 **Events and Survival by ACE Inhibitor or ARB Therapy**

Kaplan-Meier curves illustrating the survival benefits in angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) users **(dotted lines)**, compared with nonusers **(solid lines)**, on **(A)** cardiovascular (CV) events (CV hospitalization or death), **(B)** all-cause mortality, and **(C)** aortic regurgitation (AR) events (aortic valve replacement, heart failure hospitalization, or heart failure death).

events, and AR events during the follow-up period compared with patients not prescribed ACE inhibitors or ARBs. Furthermore, subgroup analyses with respect to the degree of AR, LV diastolic dimension, or the presence of LVSD did not modify the overall results. To the best of our knowledge, this is the largest retrospective observational study showing the beneficial effects of ACE inhibitor or ARB therapy in patients with at least moderate AR on all-cause mortality and CV and AR events in "real world" patients.

In our study, patients on ACE inhibitors or ARBs had a higher incidence of significant comorbidities. It is likely that the presence of diabetes, hypertension, and previous CV events may have led to the prescription of ACE inhibitors or ARBs. There were also differences in drug prescriptions in the 2 groups; more patients in the ACE inhibitor group were receiving CV medications in general, as shown in Table 1. Arguably, all these differences at baseline would, if anything, suggest that those treated with ACE inhibitors or ARBs were actually at a much higher risk compared with untreated patients. A higher rate of diuretic agent prescription, for example, may suggest a higher prevalence of symptoms of heart failure. Despite the probable higher CV risk at baseline and the higher incidence of other comorbidities, we found that patients with AR who were treated with ACE inhibitors or ARBs had better outcomes. This observed difference in outcomes remained significant even after accounting for confounding variables in both the Cox regression model and the propensity score–matched cohort analysis.

In this study, we were not able to specifically address the potential effects of vasodilators such as dihydropyridine calcium blockers, hydralazine, or nitrates because many of these drugs are prescribed concomitantly with other agents, such as calcium-channel blockers and nitrates, making it difficult to determine the specific effects of vasodilators. However, it should be noted that the choice of vasodilators has been a subject of some debate. It has been argued that vasodilators that block the RAS may be superior to other vasodilators, such as dihydropyridine, calcium-channel blockers, and hydralazine. In an animal model of chronic AR, the RAS was abnormally activated, which might suggest that blocking this system could play an important role in preventing LV dilation, hypertrophy, and loss of systolic function (21). Brain natriuretic peptide expression was almost normalized by captopril and losartan but not by nifedipine in a further study by the same group (22). Finally, these 2 drugs that block the RAS were shown to decrease the expression of fibrosis-related molecules such as collagens I and III, lysyl oxidase, transforming growth factor beta-1, transforming growth factor beta-2, and connective tissue growth factor. All these findings would suggest that RAS-targeting drugs have protective effects on the left ventricle submitted to chronic volume overload before the occurrence of systolic heart failure. With respect to clinical studies, there have not been many head-to-head comparison studies. Lin et al. (15) randomized 76 patients with chronic, mild to severe AR to either enalapril or hydralazine. Both vasodilators reduced LV mean wall stress at follow-up compared with baseline, and comparisons between groups were non-

Table 3 Study Outcomes With Adjusted HRs for the Propensity Score–Matched Cohort Analysis

Outcome Event	All Patients	ACE Inhibitors	No ACE Inhibitors	HR (95% CI)
All-cause mortality	437 (26%)	174 (20%)	263 (31%)	0.39 (0.22–0.67)
CV events (CV death and hospitalization)	724 (43%)	332 (39%)	392 (46%)	0.57 (0.41–0.79)
AR events (CHF hospitalization or AVR)	287 (17%)	134 (16%)	144 (17%)	0.73 (0.57–0.95)

Values are n (%) unless otherwise indicated.
CHF = congestive heart failure; other abbreviations as in Table 3.

significant. Neither vasodilator changed LV ejection fraction significantly. However, enalapril significantly reduced LV end-diastolic volume index, LV end-systolic volume index, and LV mass index compared with hydralazine. In another study, Banaszewski et al. (27) compared captopril with nifedipine in 25 patients with chronic, moderate to severe AR and showed that captopril but not nifedipine reduced the grade of AR. The study by Evangelista et al. (19) that investigated the effect of enalapril (20 mg/day), nifedipine (20 mg), or no treatment in 95 patients with asymptomatic severe AR found no difference in any of the groups during follow-up in the time to AVR, AR volume, or LV function on echocardiography. Similarly, a small retrospective analysis of 18 pediatric cases failed to show a benefit of ACE inhibitor therapy (28). To the best of our knowledge, no studies have examined the structural or hemodynamic effects of combined vasodilator therapy (i.e., ACE inhibitors and vasodilators) in patients with AR. Current American College of Cardiology and American Heart Association guidelines (20) recommend that ACE inhibitor therapy in patients with AR be limited to the hypertensive population, because the effects of high blood pressure in AR serve to increase afterload (29). ACE inhibitors are unlikely to directly reduce regurgitant volume, because this is dependent on the fixed regurgitant orifice area and the already reduced diastolic blood pressure (30). ACE inhibitors or ARBs may indeed deliver their beneficial effects purely by systolic blood pressure reduction, leading to reduced wall stress and improved LV systolic function (29). We did examine the effect of ACE inhibitors or ARBs on blood pressure and demonstrated no significant difference in blood pressure for those with and without ACE inhibitor or ARB therapy at baseline. This raises the possibility that the benefits of ACE inhibitors or ARBs may be independent of the presence of systolic hypertension in patients with AR. Besides these proposed direct or indirect effects of ACE inhibitors or ARBs on LV wall stress and remodeling, one should consider the possibility that the observed beneficial effects of ACE inhibitors or ARBs could simply be due to their general cardioprotective effects, as demonstrated in

Table 4 Baseline Characteristics for Propensity Score–Matched Cohort Analysis

Variable	All	No ACE Inhibitors	ACE Inhibitors	p Value (ACE Inhibitors vs. No ACE Inhibitors)
n	1,702	851 (50%)	851 (50%)	
Age (yrs)	73 (63–80)	73 (62–81)	72 (63–79)	0.18
Men	716 (42%)	352 (41%)	364 (43%)	0.56
BMI (kg/m^2)	25 (23–29)	25 (23–29)	25 (22–29)	0.48
SBP (mm Hg)	142 (130–160)	140 (131–143)	140 (130–152)	0.46
DBP (mm Hg)	73 (65–82)	75 (64–80)	75 (65–80)	0.40
Hemoglobin (mg/dl)	13 (11.7–14.1)	12.9 (11.4–14)	13 (11.8–14.1)	0.05
Cholesterol (mmol/l)	4.9 (4.13–5.72)	4.9 (4.2–5.7)	4.9 (4.1–5.8)	0.79
Creatinine (mmol/l)	98 (85–119)	98 (85–121)	99 (85–117)	0.71
LVISD (cm)	3.28 (2.8–4.0)	3.27 (2.77–3.86)	3.3 (2.8–4.1)	0.07
Diabetes	262 (15%)	129 (15%)	133 (16%)	0.78
Renal admission	44 (2.6%)	19 (2%)	25 (3%)	0.36
COPD	62 (4%)	34 (4%)	28 (3%)	0.44
Previous event	582 (34%)	286 (34%)	296 (35%)	0.61
Aspirin	918 (54%)	376 (44%)	542 (63%)	<0.01
Diuretic agents	442 (26%)	200 (24%)	242 (28%)	0.02
Beta-blockers	636 (37%)	247 (29%)	389 (46%)	<0.01
Calcium antagonists	617 (36%)	261 (31%)	356 (42%)	<0.01
Digoxin	412 (24%)	175 (21%)	237 (27%)	<0.01
Nitrates	594 (35%)	235 (28%)	359 (42%)	<0.01
Statins	752 (44%)	264 (31%)	488 (57%)	<0.01
LV impairment	763 (45%)	381 (45%)	382 (45%)	0.96

Values are n (%) or median (interquartile range).
Abbreviations as in Table 1.

Table 5 Adjusted HRs for the Impact of ACE Inhibitors or ARBs on Outcomes Stratified by the Severity of Regurgitation

Severity of AR	n	All-Cause Mortality HR (95% CI)	CV Events HR (95% CI)
Moderate	1,803	0.58 (0.47–0.72)	0.79 (0.68–0.93)
Severe	463	0.4 (0.24–0.66)	0.70 (0.50–0.98)

Abbreviations as in Table 3.

outcome trials of at-risk populations, such as the HOPE (Heart Outcomes Prevention Evaluation) (31), SOLVD (Studies of Left Ventricular Dysfunction) (32), SAVE (Survival and Ventricular Enlargement) (33), and AIRE (Acute Infarction Ramipril Efficacy) (34) studies. Obviously, any indication that the observed outcomes in our study are due to the direct or indirect effects of ACE inhibitor or ARB therapy on ventricular wall stress and remodeling or a general cardioprotective effect is purely speculative and cannot be inferred directly from this retrospective observational study.

Study limitations. We recognize the inherent limitations that come with a retrospective, nonrandomized, observational study. However, the present study reflects the true population and a real-world scenario and is unique in comparison with other previous studies because of our large number of patients with varying degrees of AR, but most importantly because we found that ACE inhibitors or ARBs reduce all-cause mortality and CV events in patients with AR. We have also accounted for the baseline differences and the influence of potential confounders by performing a multivariate analysis for the outcome and a propensity score–matched cohort analyses.

In common with all observational studies, it was impossible for our study to account for unknown confounding influences that may have biased the observed differences between the groups considered. In particular, we had little information regarding symptomatology, and one may surmise that the patients receiving ACE inhibitors were more likely to be symptomatic. However, symptoms are an adverse prognostic sign in AR and would, if anything, mitigate the benefit we saw with ACE inhibitors. Additionally, those treated with ACE inhibitors were slightly younger (mean age 69.9 years vs. 72.0 years), making it possible that these differences could have accounted for the better outcomes observed in those who had been treated with ACE inhibitors.

We recognize that our observed benefits of ACE inhibitors or ARBs in relation to AR events were largely driven by heart failure endpoints of heart failure hospitalization and death given the limited number of AVRs. Another limitation is that the echocardiographic database details overall assessment of severity of AR by accredited sonographers as mild, moderate, or severe and does not consistently report the measures of regurgitation directly. This, combined with the lack of standardized echocardiographic follow-up data, limited our ability to reliably determine the effects of ACE inhibitor or ARB therapy on the progression of aortic valve disease. Clearly, a large randomized placebo-controlled trial would be required to provide definitive evidence and further define the underlying mechanisms of the benefit of ACE inhibitors in patients with AR.

Conclusions

These are the only retrospective outcome data on the use of ACE inhibitor or ARB therapy in AR, and we have shown that the prescription of ACE inhibitors or ARBs is associated with reduced all-cause mortality and CV and AR outcomes in patients with moderate to severe AR. Our data need to be confirmed by a prospective randomized controlled outcome trial.

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Reprint requests and correspondence: Prof. Chim C. Lang, Centre for Cardiovascular and Lung Biology, Ninewells Hospital and Medical School, University of Dundee, Dundee DD19SY, United Kingdom. E-mail: c.c.lang@dundee.ac.uk.

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